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09/844,508	04/27/2001	Alan P. Wolfe	8325-0014	9058
23419	7590	02/25/2004	EXAMINER	
COOLEY GODWARD, LLP 3000 EL CAMINO REAL 5 PALO ALTO SQUARE PALO ALTO, CA 94306			AKHAVAN, RAMIN	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Applicant

02/23/04 RA

## Office Action Summary

Application No.

09/844,508

Applicant(s)

WOLFFE ET AL.

Examiner

Ramin (Ray) Akhavan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 05 December 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-6, 8, 10-13, 17-33 and 43-70 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-6, 8, 10-13, 17-33 and 43-70 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 03/11/2003.
- 4) ☒ Interview Summary (PTO-413)  
Paper No(s)/Mail Date 02/23/04.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

## **DETAILED ACTION**

### ***Continued Examination Under 37 CFR 1.114***

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/05/2003 has been entered. The claims pending are 1-6, 8, 10-13, 17-33 and 43-70.

### ***Response to Amendment***

Applicant's arguments, see Remarks, filed 12/05/2003, with respect to rejections under § 112, Written Description, Second Paragraph, § 102(e) and § 103 have been fully considered and are persuasive. The previously made rejections have been withdrawn.

Applicant's arguments, see Remarks, pp. 9-10, with respect to the Obviousness-Type Double Patenting (viz., co-pending Application No. 08/942,087) have been fully considered but they are not persuasive. Therefore rejection of claims 1-6, 8, 10-13, 17-33 and 43-70 under 35 U.S.C. § 101 is maintained for reasons of record and as discussed below.

### ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed.

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Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

**1. Claims 1-6, 8, 10-13, 17-33 and 43-70 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S.**

**Application No. 09/942,087.**

Applicant asserts that the instant claims are directed to methods in which a subunit protein (or functional fragment thereof) from a multi-protein chromatin remodeling complex is used (in a fusion protein) to alter chromatin structure (i.e. chromatin remodeling), not to regulate gene expression. Furthermore, applicant asserts that the claims of co-pending application 09/942,087 are drawn to a method of regulating gene expression, where fusion proteins directly modulate gene expression, thus distinguishable from fusion proteins of instant application. (Remarks, p. 10, l. 1). In short, the instant claims are drawn to a method for altering chromatin structure where a fusion protein facilitates activation, whilst the reference claims are drawn to a method for "regulation of gene expression" where a fusion protein facilitates regulation. Put another way, applicant asserts that it is improper to equate the terms, "facilitating activation" with "regulation of gene expression". (Id. at first full ¶). While applicant makes a rational argument, it does not answer in the negative the salient question, do the reference claims anticipate the instant claims. Indeed the answer is yes because modifying chromatin structure is

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a prerequisite for modulation of gene expression. In other words, while chromatin accessibility may not be sufficient for regulation of transcription, it certainly is necessary for such regulation.

When comparing, for example, reference claim 1 and 13, compared to instant claims 1, 12 and 13, the relationship between the chromatin structure and modulation of expression is further clarified. Instant base claim 1 and dependent claims 12-13 are drawn to a method of altering chromatin structure, targeted to a specific gene by art-recognized DNA-binding protein (i.e. zinc finger protein) motifs contained in a fusion protein, where the fusion protein also contains at least a subunit (or functional fragment) from any chromatin remodeling complex, with the end result being modulation of gene expression.

Furthermore, the claims are directed to contacting the target region with the fusion protein, wherein the contacting ultimately results in altered chromatin structure.

Reference claim 1 is drawn to a method of modulating gene expression where a fusion protein comprising a targeting motif (i.e. zinc finger protein) and a “functional domain”, where the fusion protein binds (i.e. contacts) the target region thereby modulating gene expression. Furthermore, reference dependent claim 13 is drawn to chromatin structure altering proteins (e.g. DNMT). Therefore the reference claims are drawn to alteration of chromatin structure as directed to modulation of gene expression. Against the backdrop that chromatin remodeling may modify transcription, replication, repair or integration, the reference claims are at minimum a species or sub-genus of the instant claims (i.e. chromatin modification leading to expression, repair or integration).

Therefore, a patent to the genus would, necessarily, extend the right of the species or sub-genus should the genus issue as a patent after the species or sub-genus. Indeed, although

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alteration of chromatin may be involved in other cellular processes, chromatin remodeling is certainly a prerequisite in modulation of transcription. (See Peterson, CL. Curr. Opin. Genet. Dev. 1996; 6(2):171-5, at Introduction, p. 171; Felsenfeld and Groudine. Nature, 2003; 421:448-53, at ¶ 4, p. 449). Filing of a terminal disclaimer will obviate this rejection.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

- 2. Claims 1-6, 8, 10-13, 17-33 and 43-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* modification of chromatin, does not reasonably provide enablement for *in vivo* application. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.**

The test for enablement is whether one skilled in the art could make use the claimed invention from the disclosure in the specification coupled with information known in the art without undue experimentation. *United States v Telectronics Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor but instead is a conclusion reached by weighing many factors which are outlined in *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). The factors include the following:

**Scope/Breadth of the claims.** The broadest claims read on a method of altering any cell's chromatin structure, thus read on both *in vitro* and *in vivo* application of the method claimed. Furthermore, the invention is directed to altering chromatin structure using any subunit from any chromatin remodeling complex.

**Nature of the invention.** The invention is drawn to a method of altering a cell's chromatin structure by using a fusion protein with a targeting component (i.e. zinc finger DNA binding domain) and a component consisting of at least one subunit with a chromatin remodeling function. Furthermore, the invention is drawn to either *in vitro* or *in vivo* use. Furthermore, to the extent that the invention is drawn to *in vivo* use, the invention is necessarily directed to gene therapy (e.g. altering DNA expression patterns), because whether the fusion protein is administered through a gene altering or non-gene altering vector (e.g. viral or liposomes), the method is directed to accessing chromatin in the nucleus of the cell and results in altered gene expression, for example. The only disclosed utility for such *in vivo* emdodiments is for therapeutic effect.

**State of the art.** With respect to *in vivo* chromatin structure modification, "[C]hromatin in mammalian cells remains relatively poorly understood... due to... the complexity of the chromatin remodeling machinery, and the dynamic properties of chromatin *in vivo*." (Urnov et al. EMBO rep. 2002; 3(7) :610-15, at 610, Abstract). Notably, the primary thrust of the work in the art is directed to regulation of gene expression, perhaps because the chromatin remodeling machineries, whether involved in transcription, replication or DNA repair are physically and functionally linked. (Morales et al. Biochimie, 2001 ; 83(11-12) :1029-39, at 1038). Moreover,

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different multi-protein-subunit remodeling complexes may regulate only a subset of genes *in vivo*. (e.g., Armstrong et al. Cell, 1998; 95:93-104, at 102).

Moreover, even with respect to remodeling complexes where subunits have been somewhat characterized viz., function, “Many questions remain regarding the specific functions of these subunits, their organization with the complexes, and how they work together to accomplish their task”. (Wang, W. Curr. Top. Microbiol. Immunol., 2003; 274:143-69, at 156). In sum the state of art with regard to characterization of complexes, their subunits and their affects/function *in vivo* is in the early stages of development.

With respect to the state of art in Gene Therapy, “[T]here is still no conclusive evidence that a gene-therapy protocol has been successful...”. (Anderson, F. Nature, 1998; 392:25-30).

**Unpredictability of the art.** With regard to *in vivo* modification of chromatin structure, based on the state of the art, it would highly unpredictable whether a fusion construct once administered to an animal, would first, evade the immune system, and second, not impart unintended deleterious effects (e.g. toxicity or remodeling non-target sites). For example, as the functionality for the many subunits of the many multi-protein remodeling complexes, remains to be elucidated, even if the fusion construct is effectively targeted, the subunit imparting remodeling function may not actually work on the target gene *in vivo*. In addition, functionality *in vitro* does not necessarily translate into functionality *in vivo*, with respect to the broad class of remodeling complexes claimed.

In addition, as the invention is broadly drawn to any remodeling complex, be it those that either function as motors to disrupt nucleosomes (e.g. ATP-driven) or as enzymatic machinery to modify histones chemically (e.g. acetylases and deacetylases), there would be a heightened



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degree of unpredictability, because each complex functions through distinctly different mechanism. Furthermore, each mechanism could be part of a complex system of pathways involved in different cellular processes (e.g. replication or DNA repair), where introduction of applicant's fusion protein may disrupt pathways in a way so as to have deleterious effects. Thus while the intended purpose *in vivo* would be to provide access to DNA (i.e. remodel chromatin) for one purpose, an unintended downstream outcome might result, such as modifying expression of an unintended target gene. With respect to certain mechanisms of chromatin remodeling, for example, such as ATP-driven remodeling complexes, it is not known how or by what mechanism chromatin is remodeled, thus there is greater unpredictability for *in vivo* applications; "[T]he mechanistic basis for how [remodeler] SWI/SNF uses the energy of ATP hydrolysis to alter nucleosome structure has remained a major unsolved mystery." (Peterson and Workman. *Curr. Opin. Genet. Dev.* 2000; 10(2):187-92, at 187).

With respect to unpredictability in gene therapy, the art is still a highly unpredictable area within biology and medicine. For example, vectors used to deliver fusion constructs encoding therapeutic products may be erroneously inserted into a particular gene resulting in unknown, adverse or detrimental effects. (See, Check, Erika, Feb. 13, 2003, *Nature*, 421: 678) (citing occurrence of leukemia due to insertion of retroviral vectors used in gene therapy into a particular stretch of DNA); (See also, Juengst, ET. June 2003, *BMJ*, 326:1410-11) (indicating that gene transfer often has multiple and unpredictable effects on cells).

**Amount of guidance provided.** There is guidance provided with respect to making the fusion constructs. Aside from prophetic generic suggestions on gene transfer methods (e.g.,

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Spec. pp. 38-39), there is little guidance on how to use the invention, a process of altering chromatin structure *in vivo*.

For there to be sufficient guidance, the disclosure would have to teach how to deliver the fusion protein *in vivo* to circumvent potential toxicity, an adverse immune response, as well as potential unintended targeting (e.g. activating non-target chromatin containing non-target genes). The disclosure does not provide significant guidance on how to use the invention *in vivo*.

**Number of working examples.** All examples provided are *in vitro* (e.g. HeLA cells and 293 cells).

**Amount of Experimentation Required.** The level of skill in the art required to practice the claimed invention is high. Given the unsolved hurdles to successful practicing of the invention, the level of unpredictability in the art and lack of working examples, it must be considered that the skilled artisan would be required to conduct trial and error experimentation of an undue nature in order to attempt to practice the claimed invention commensurate with the scope of the claims.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

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claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**3. Claims 1-6, 8, 10 and 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cox, III et al. (U.S. Patent No. 6,607,882 B1; hereinafter Cox), further in view of Hsieh (Mol. Cell. Biol. 1994; 14(8): 5487-94).**

The claims are drawn to method of altering chromatin structure, where a fusion protein comprising a zinc-finger DNA binding motif and a second motif from a chromatin remodeling complex is contacted with cellular chromatin.

Cox teaches a method for modulating expression of endogenous cellular genes, which necessarily comprises remodeling of chromatin structure using recombinant zinc finger proteins. More specifically the zinc finger protein or ZFP (e.g. VEGF 3a/1) is fused with a transcriptional activator (i.e. KRAB) or transcriptional repressor. (e.g. Fig. 5; depicting ZFP-KRAB fusion protein). In addition, Cox teaches, that the regulated endogenous genes can be from any source (e.g. animal, plant and protozoan), where the genes are in the native chromatin state (i.e. active or nonactive). (e.g. col. 10, ll. 52-55).

Cox does not specifically illustrate that the fusion protein can comprise a subunit from a specific chromatin remodeling complex.

However, Cox explicitly teaches that the transcriptional activator (or repressor) comprising the fusion protein can be substituted with “endonucleases, integrases, recombinases, methyltransferases (i.e. methylation), histone acetyltransferases, histone deacetylases...”. (e.g. col. 12, ll. 40-45). This an explicit motivation to modify the fusion construct with a chromatin remodeling subunit (i.e. methyltransferase).

Hsieh teaches that CpG methylation (i.e. alteration of chromatin structure) leads to significant inhibition of gene expression. (e.g. Abstract)

It logically follows, that it would have been obvious to produce a fusion protein comprising a ZFP and a chromatin remodeling motif, such as a methyltransferase, with the expected benefit of broader application of proteins or effector domains that have the ability to modulate transcription via different mechanisms. Indeed applicant’s example illustrating regulation of expression is exactly what Cox teaches: a fusion construct with a methyltransferase (i.e. DNMT) used to repress gene expression. (e.g. Example 13).

Given the teachings of the cited art and the level of skill of the ordinary skilled artisan at the time of the invention and applicant’s own data, it must be considered that there would have been a reasonable expectation of success, in modifying the fusion protein to comprise a protein or effector domain that alters chromatin structure (e.g. methyltransferase).


### ***Conclusion***

No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday- Friday from 8:30-5:00. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
GERRY LEFFERS  
PRIMARY EXAMINER